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Challenges of Rabies

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Abstract: Rabies has one of the highest case-fatality ratios of any infectious disease, almost always fatal, caused by lyssavirus infection. It is associated with dysfunction of the neurons after the entrance of rabies virus to the central nervous system, usually in the spinal cord. The bite route is still regarded as the most important means of transmission. Although wild animals are regarded as a host for rabies, dogs and cats remain the most important sources of human exposure. The disease is worldwide in distribution except in Antarctica. The most affected regions are tropical countries in Africa, Asia and South America, which have limited resources for diagnosis, treatment, control surveillance and vaccine production and improvement. Controlling rabies is challenging, due to wide host range and worldwide distribution, availability of many free roaming/stray dogs and lack of awareness about the disease. Diagnosis of the rabies is one of the most difficult duties because of non-specific clinical symptoms, long incubation period and limited diagnostic techniques. Vaccines are expensive and consequently, out of the reach for many people. Apart from high cost and unavailability, they are associated with serious neurologic complications. The economic costs of rabies in a country are associated with vaccinations, laboratory diagnosis, treatment and public education. So, the main objectives of this paper are to highlight the general characteristics of rabies virus, indicate the overall course of rabies and review possible challenges of rabies.

Key words: Challenges of rabies · Rabies

INTRODUCTION

The dictionary tells us that rabies is derived from the Latin rabere, “to rage or to rave”, as is the corresponding adjective rabid; rabere possibly may have earlier origin in the Sanskrit rabhas, for “violence”. The Greeks adopted their own word, Lyssa meaning “madness”, for rabies; this in turn is still reflected in English in Lyssophobia, described in the oxford English Dictionary as “a morbid dread of hydrophobia, the symptoms of which sometimes simulate those of the actual disease”. Not surprisingly, then, it is the image of the mad dog that has for centuries past come to symbolize human kind’s fear of the disease as expressed by writers, legislators and medical practitioners and philosophers. “Mad” or “vicious” dogs began to appear in the legal documents in Mesopotamia as early As 2300 B.C [1].

Rabies is an acute, almost inevitably fatal zoonotic disease. It has worldwide distribution. Humans and nearly all mammals are susceptible. Beside poliomyelitis and pox, rabies is one of the longest known infectious diseases in human history [2]. Rabies virus usually is transmitted from animal to animal through bites. The incubation period is highly variable. In domestic animals, the incubation period is generally 3–12 weeks but can range from several days to months, rarely exceeding 6 months [3].

Rabies has probably existed in the parts of Africa for centuries as it was reported by European travelers to Ethiopia and South Africa in the eighteenth and early nineteenth centuries. Among Bantu of South Africa, rabies in spotted genets leads to the belief that these animals had poisonous saliva. Rabies has long been familiar to the Ndebele people of Zimbabwe and to the

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inhabitants of south kavirondo in Kenya. The infection was reintroduced by dogs imported by the European settlers [4].

Although rabies is primarily a disease of dogs in Ethiopia, other domestic and wild animals have also been affected. It is also a common problem among human population because of high rate of man to dog contact [5]. There is however, lack of information to determine the magnitude of rabies in man and other domestic animals in the country [6].

Human rabies vaccine has a long history beginning with the first anti-rabies treatment developed by Pasteur, Roux and their colleagues in 1885. All rabies vaccines that immediately followed the original Pasteur treatment were produced and applied using the same theory of serial injections of increasingly virulent rabies virus-infected nerve tissue. World Health Organization (WHO) recommended that this type of rabies vaccine to be discontinued because this contained residual, live, fixed rabies virus, which has a chance of reversion and cause partial paralysis [1].

Many factors help to explain the relative lack of success of vaccination campaigns in developing countries, as compared to developed countries. For example, the campaigns are not always well managed; vaccination does not cover a sufficient number of animals, nor does it reach all communities; and the vaccines themselves are not always handled or applied correctly. The wide biodiversity present in many developing countries also complicates rabies control, because it increases the number of possible reservoirs of the rabies virus. This condition favors the 'spillover' phenomenon from wild reservoirs to domestic animals, such as dogs [7].

Approaches that has been successful in controlling rabies in developed countries have not been applied successfully in developing countries for a variety of reasons, including high costs, lack of adequate infrastructure for management of dog rabies, wide spread prevalence of feral dogs and cultural and religious objections to various animal control measures [8]. Ethiopia being one of the developing countries is highly endemic for rabies and facing to different challenges of rabies [9].

Therefore, the objectives of this communication was:

- ✓ To highlight the general characteristics of rabies virus.
- ✓ To indicate the overall course of rabies.
- ✓ To review the possible challenges of rabies.

Etiology: Rabies is caused by neurotropic *rabies virus* which is prototype species of the genus *lyssavirus* (from the Greek lyssa, meaning "rage") in the family *Rhabdoviridae* (from the Greek rhabdos, meaning "rod"). It has helical symmetry and a bullet like shape with a length of about 180 nm and a cross-sectional diameter of about 75 nm. One end is rounded or conical and the other end is planar or concaves [10]. It is in many ways considered a close relative of prototype species vesicular stomatitis virus of the genus *vesiculovirus*, in the same family, since, it shares a similar morphology, chemical structure and life cycle and it can infect mammalian (animal and human) hosts, invariably causing a fatal encephalomyelitis [11].

The family *Rhabdovirdae* together with the families *paramyxovirdae, Filoriridae* and *Bornaviridae* constitute the "super family" taxon, order mononegavirales, because all member of the order are ribonucleic acid (RNA) viruses that contain non-segmented, negative sense, single – strand RNA genomes [12].

Closely related lyssaviruses, which are known as rabies related lyssaviruses or non-rabies lyssaviruses, can cause a neurological disease identical to rabies. Lagos bat virus, Duvenhage virus, European bat lyssavirus (EBLV) 1, EBLV 2, Australian bat lyssavirus (ABLV), Mokola virus and Irkut virus have caused clinical cases in humans or domesticated animals and Ikoma virus was detected in the brain of an African civet (*Civettictis civetta*) with neurological signs. Shimoni bat virus, Aravan virus, Khujand virus, Bokeloh virus and West Caucasian bat virus have been found, to date, only in bats, but might be pathogenic in other species [13].

Additional rabies-related lyssaviruses are likely to exist. Rabies virus and the rabies-related lyssaviruses have been classified into two or more phylogroups, based on their genetic relatedness. Viruses that are more closely related to rabies virus can be neutralized, at least to some extent, by antibodies to rabies virus. Phylogroup I contains rabies virus, Duvenhage virus, EBLV 1, EBLV 2, Australian bat lyssavirus, Irkut virus, Aravan virus and Khujand virus. Bokeloh virus also appears to belong to this group. Phylogroup II consists of Lagos bat virus, Mokola virus and probably also Shimoni bat virus. West Caucasian bat virus has been provisionally placed in a new group, phylogroup III. Ikoma virus seems to be related to West Caucasian bat virus, although a full analysis is not yet available [13].

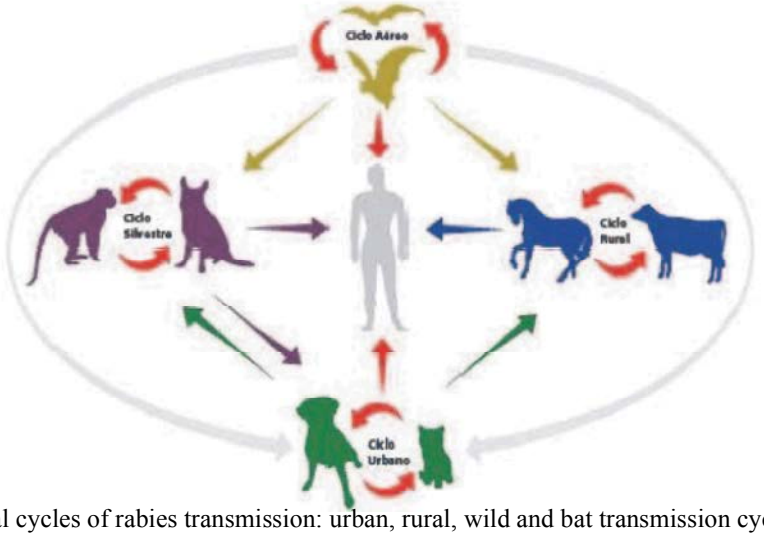

Fig. 1: Epidemiological cycles of rabies transmission: urban, rural, wild and bat transmission cycles. Source: [16]

Table 1: Rabies-related lyssaviruses; their serotype, host ranges and geographical distribution.

Serotype	Host	Geographical occurrence
Rabies virus (Lyssavirus type 1)	Canids, raccoons, skunks etc	World wide
Lagos bat virus (Lyssavirus type 2)	Fructivorous bats	Africa
Mokola virus (Lyssavirus type 3)	Fructivorous bats	Africa
Duvenhage virus (Lyssavirus type 4)	Fructivorous bats	South Africa
European bat virus type 1 (Lyssavirus type 5)	Insectivorous bats	Europe
European bat virus type 2 (Lyssavirus type 6)	Insectivorous bats	Europe
Australian bat virus (Lyssavirus type 7)	Flying foxes	Europe

Source: [2].

All the lyssaviruses share many biological and physicochemical features as well as amino acid sequence characteristics that classify them with other rhabdoviruses. These include the bullet shaped morphology helical nucleocapsid or ribonucleoprotein core, RNA genome structure and organization and structural proteins of the virus. The five structural proteins of the virion include nuclcocapsid protein, phosphoprotein (P), matrix protein (M), glycoprotein (G) and RNA – dependent RNA polymerase or large protein (L) [1].

Epidemiology

Transmission: Transmission of both wild and urban rabies occurs mainly when an animal that is shedding virus in its saliva bites another susceptible animals or humans [14]. Spread of the disease is often seasonal, with high incidence in late summer and autumn because of large scale movement of wild animals at the mating time and in pursuit of food [15].

Until a few years ago it was considered three transmission cycles (urban, rural and wild) and is currently included another cycle observed among bats, denominated the air (Figure 1). Rabies is an urban problem in developing countries is characterized by the presence of disease in domestic animals such as pet dogs and cats. Rabies is mainly rural transmitter the hematophagous bat (*Desmodus rotundos*) that transmits the disease to herbivores, as these are the most common food source. Cycle in wild disease is transmitted to animals like fox, wolf, monkey, coon, skunk, among others. These animals can be a source of food for the hematophagous bat. It can capture bats and suffer injury or attacked by domestic animals. The air cycle is important for virus among species of bats, because these are the only mammals that fly [16].

Rabies in Developing World: Most deaths from rabies occur in developing countries with inadequate public health resources and limited access to preventive treatment. These countries also have few diagnostic facilities and almost no rabies surveillance. Underreporting is a characteristic of almost every infectious disease in developing countries and increasing the estimated human mortality does not in itself increase the relative public health importance of rabies. There is, however, one often neglected aspect of rabies that does affect perception of its importance [17].

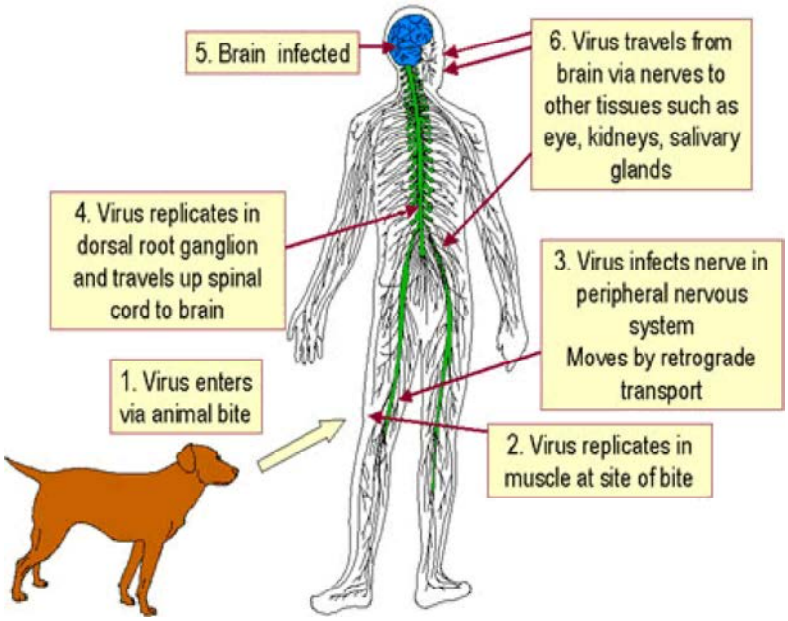

Fig. 2: The overall pathogenesis and spread of rabies virus from the site of bite to brain and then other parts of the body

Rabies remains endemic throughout the world except in certain Western European countries and in number of islands, but more than 99% of all human rabies deaths occur in the poorest developing countries [18]. Recorded deaths in developing countries probably provide a gross underestimate of the true situation as these areas generally have notoriously poor notification systems. Reasons underlying the preponderance of rabies cases in poor countries are complex but include opposing needs and limited resources for veterinary control, the prohibitive cost of post-exposure vaccine and immunoglobulin, poorly informed communities, inadequately trained health and veterinary staff and inaccessibility of health-care facilities [19].

The use of nonsterile needles and syringes for rabies vaccination also poses a risk for transmission of blood-borne pathogens, such as HIV, hepatitis B and hepatitis C in many of these countries. Of considerable concern is the re-emerging status of rabies in Africa [20]. This trend has been attributed to rapid population growth with parallel dog population growth directed by security concerns, for example a growth of 7% in the dog population in Zimbabwe between 1954 to 1986, mobility of human populations, particularly political refugees, high rates of urbanization and a disintegration of veterinary rabies control [21]. The latter is of particular importance as dog rabies vaccination is a more cost-effective measure for preventing human rabies than reliance on post-exposure prophylaxis for dog-bite victims [22].

Pathogenesis: Rabies virus gains entry into a new host by introduction of virus-containing saliva into a bite wound. Entry may also be gained by saliva contamination of the mucous membranes of the mouth eyes and nasal passages. The virus does not penetrate intact skin [23]. At the site of entry, there may be local viral proliferation in non-neural tissue followed by viral attachment to nerve cell receptors and entry into peripheral nerve endings [24].

The virus is transported along afferent axons, eventually reaching the central nervous system where proliferation is followed by widespread distribution of the virus throughout the brain and spinal cord. Following centrifugal transport along efferent cranial nerves, the salivary glands become infected and virus particles are shed in the saliva. Infection of the brain commonly leads to behavioral changes that induce the host to bite other animals, thereby transmitting the virus. The clinical picture can be highly variable between different species, in individuals of the same species and even within the course of the disease in a particular individual. The widespread central nervous system infection almost inevitably leads to death, usually through respiratory paralysis, but also through secondary circulatory, metabolic or infectious processes [25].

The incubation period varies with the amount of virus transmitted, virus strain, site of inoculation (bites closer to the head have a shorter incubation period), host immunity and nature of the wound. In dogs and cats, the incubation period is 10 days to 6 months; most cases become apparent between 2 weeks and 3

months. In cattle, an incubation period from 25 days to more than 5 months has been reported in vampire bat-transmitted rabies [26].

Clinical Signs: The clinical signs of rabies are rarely definitive. Rabid animals of all species usually exhibit typical signs of CNS disturbance, with minor variations among species. The course may be divided into 3 phases namely prodromal, excitative and paralytic or end stage. However, this division is of limited practical value because of the variability of signs and the irregular length of the phases. During the prodromal period which lasts approximately 1-3 days, animals show only vague central nervous system signs, which intensify rapidly. The term "furious rabies" refers to animals in which aggression (excitatory phase) pronounced. The animals become irritable and with the slightest provocation, may viciously and aggressively use its teeth, claw, horns or hooves. Paralytic form is first manifested by paralysis of the throat and masseters muscle often with profuse salivation and in ability to swallow: Hydrophobia [27].

Diagnosis: By history of animal exposure [28]. The recommended laboratory procedure includes the following tests [15]. Fluorescent antibody test (FAT) on the impression smears from the brain current recommendations includes sampling of the hippocampus, medulla oblongata, cerebellum or gasserian ganglion. Enzyme linked immunosorbent assay (ELISA) is available for the detection of rabies antigen in animals. Histological search for negribodies in tissue sections with results available in 48 hours. Because of false positive diagnosis the technique is in some disrepute.

Treatment: Post exposure prophylaxis consists of immediate wound cleansing and disinfection, followed by rabies vaccination and the administration of human rabies immunoglobulin. The rabies vaccine is given as 5 doses in United States and it is usually administered intramuscularly in the arm. Fewer doses and no rabies immunoglobulin are given if the person was previously vaccinated. Post exposure prophylaxis is highly effective if it is begun soon after exposure. There is no effective treatment once the symptoms develop. Vaccines, antiviral drugs such as ribavirin, interferon-alpha, passively administered anti-rabies virus antibodies (human immunoglobulin or monoclonal antibodies), ketamine and/or the induction of a coma have been tried in the past, but were usually ineffective [29].

Control and Prevention: Domestic animal vaccination: Multiple vaccines are licensed for use in domestic animal species. Vaccines available include inactivated or modified live-virus vectored products, products for intramuscular and subcutaneous administration, products with durations of immunity from 1 to 4 years and products with varying minimum age of vaccination [30]. Animal control: All local jurisdictions should incorporate stray animal control, leash laws, animal-bite prevention and training of personnel in their programs [31]. Public health education: Essential components of rabies prevention and control include ongoing public education, responsible pet ownership, routine veterinary care and vaccination and professional continuing education [27].

Challenges of Rabies

Control Challenges: We can't control rabies because of the 5 major challenges to be overcome [32].

- Rabies is considered a low priority for public health and veterinary services.
- There are too many free-roaming/stray dogs that cannot be vaccinated. Turn-out at vaccination points would be too low to vaccinate sufficient dogs to control rabies.
- We don't have enough information on dog ecology and dog population sizes.
- There are many different wild animal species that can be sources of infection.
- We don't have sufficient resources to vaccinate enough dogs.

In Africa, rabies is often handled separately by health and veterinary authorities and confusion about who is responsible for controlling the disease is common [33]. In 2010, Lembo *et al*. [34] identified four common reasons for the lack of effective canine rabies control in Africa:

- A low priority given to disease control as a result of the lack of awareness of the rabies burden
- Epidemiological constraints, such as uncertainties about the required levels of vaccination coverage and the possibility of sustained infection cycles in wildlife.
- Operational handicaps, including the accessibility of dogs for vaccination and insufficient knowledge of dog population sizes when planning the vaccination campaigns.
- Limited resources for the implementation of rabies surveillance and control.

Wide Host Range and Worldwide Distribution: Rabies virus has a wide host range. All warm – blooded animals including humans can be infected [35]. The disease is caused by viral representatives in the genus *lyssavirus*, family *Rhabdoviridae*. Rhabdoviruses as a group can replicate in vertebrates, invertebrates and plants. Mokola is the only lyssavirus considered to be able to replicate in insect cells. Similarly, rabies virus can replicate *in vitro* in certain cold-blooded vertebrate tissue, but no successful *in vivo* attempts have been reported [36]. It has high plasticity, adaptability and persistency, as evidenced by its wide spread occurrence in plants, invertebrates, fish, amphibians, reptiles and mammals. More than 4000 mammalian species are susceptible to rabies [1].

Key among the many challenges implicit in rabies control is the pervasiveness of the translocation of raccoons and other mesocarnivores [37], intentional or accidental, which represent a common extrinsic threat for both local and long-range movement of rabies and control programs [38]. Although translocation has been instrumental in specific endangered species recovery efforts and for other conservation purposes, large numbers of raccoons, skunks and other species are purposefully moved about the landscape as a part of rehabilitation and nuisance wildlife control efforts [37].

Traditionally, dogs and cats have been the main source of animals. However, native fauna, including foxes, skunks, wolves, coyotes, vampire, insectivores and fruit eating bats, raccoons, mongoose and squirrels provide the major source of infection in countries where domestic carnivore are well controlled. Rabies occurs in all warm-blooded animals. The disease occurs in cattle, sheep, pigs and in horses in most countries that exclude it by rigid quarantine measures or prohibition of the entry of dogs. However, the genus *lyssavirus* can still cause surprises. In 1996 and 1998, two women died of rabies in Queensland, Australia, from infections with a newly discovered rabies-related virus (Australia bat lyssavirus). In 2002, a man died in Scotland after contracting European bat lyssavirus rabies indicating that after a century of freedom from rabies, the disease is enzootic in United Kingdom [15].

Lack of Awareness: There is lack of awareness about rabies among the public. The laissez -faire attitude towards rabies by Americans cause instances of rabies exposure. A survey of middle school children in Texas found lack of basic knowledge about rabies as only 0.3% of children achieved a minimum score of 75% on a survey of knowledge about rabies. Respondents lacked knowledge about the disease transmitted and less than one- third were even aware of rabies epidemic in Southern Texas, despite the fact that the rabies epidemic has been occurring in southern Texas for the previous 15 years [15].

Post exposure prophylaxis is unlikely to be sought after lick-associated exposures to dogs. Some cultures are known to believe that the lick from a dog is useful for wound treatment [39]. In conjunction with this belief, some cultures believe that the aggressive and uncharacteristic behavior of persons or animals with symptoms of rabies is caused by sorcery or demon possession. Far too often rabies patients end up at tribal or traditional healers whose treatments include exorcism, administration of toxic herbs and other such undesirable interventions [40]. Many human deaths occur in developing countries because victims of dog bites do not seek medical treatment [1].

In India, there are about 17 million animal bites cases every year. India alone constitutes about 40 percent deaths due to rabies in the world. Out of these, there are about 20,000 deaths due to rabies and most of these are caused due to stray dog bites. Despite such an alarming situation, there is lack of information, communication and awareness on rabies. In fact, there is lack of awareness even among physicians and victims of animal bites are not being treated properly in the country. Instead of getting serum (rabies immunoglobulin) along with anti-rabies vaccines, the victims are being treated with anti-rabies vaccines only. In Chandigarh, there are about 600 reported cases of animal bites every month. However, the biggest flaw is that no treatment facility for animal bites is available at health centers across rural areas of the country [41].

In Africa, In the case of domestic dog vaccination, socio-economic and cultural factors, including religious and other beliefs, are likely to influence dog human relationships, which – in addition to low community awareness and attitudes towards rabies and dogs can compromise dog vaccination programs [7].

Study in KwaZulu-Natal, South Africa shows, about eighty-six percent of the population surveyed across the province had at least heard of the disease even if they are unaware of the details surrounding transmission and consequences of exposure. Some respondents stated that they did not truly know the source of rabies or how to prevent it. Some respondents knew that vaccination of dogs was important to the safety of people in the community [42]

Study in Addis Ababa, Ethiopia shows, only small proportion of respondents claimed to possess the basic knowledge of what rabies is and that it is a deadly disease. Only thirty four percent of the study respondents were able to identify most recognized clinical signs of the disease both in animals and human [43]. In Ethiopia individuals who are exposed to rabies virus often see traditional healers for the diagnosis and treatment of the disease. These widespread traditional practices of handling rabies cases are believed to interfere with timely seeking of PEP. Rabies victims especially from rural areas seek PEP treatment after exhausting the traditional medicinal intervention and usually after a loss of life from family members [44].

Stray Dogs: Third world countries do not have the means to control stray dogs that transmit urban rabies. Rules of religion may prevent measures being taken against stray dogs, as the case in India [2]. Exposure to rabid dogs is still the cause of over 90% of human exposures to rabies and of over 99% of human deaths worldwide [17].

Worldwide, domestic dogs accounted for most of human rabies deaths and post exposure prophylaxis. In less developed nations, where dog rabies has not been controlled, the prevalence of canine and human rabies is quite high [45]. In Latin America and Asia, this feature is a problem because of the existence of many stray dogs; unvaccinated dogs and absence of rabies control programs. These two factors are responsible for thousands of rabies cases in dogs in these countries [31]. In most Asian countries, free-roaming dogs are well known to the communities who look after them, especially in suburban and rural areas, but the level of care may be influenced by culture or religion. Community dog populations represent the majority of dogs, so that human interaction with this type of dog population is common [7].

Eshetu *et al*. [5] reported that all available data indicate that dogs are responsible in maintaining as well as dissemination of rabies in Ethiopia and are primary cause for fatal human rabies cases. Although many ill dogs were not brought for examination, the actual numbers of rabid dogs in Addis Ababa are expected to be higher in comparison to the large number of stray dogs roaming around in the street. On the other hand, there was no significant peak in the monthly distribution of rabid dogs. This information suggests that dogs appear to bite people at constant rate throughout the year with constant risk of contracting rabies by humans from the bite of these dogs.

Diagnosis Challenges: The diagnosis of rabies is one of the most difficult and important duties that a veterinarian is called upon to perform. Since in most cases there is a probability of human exposure, failure of recognizing the disease may place human life in jeopardy. It is not even sufficient to say that if rabies occurs in the area one will classify every animal showing nerves signs as rabid because nerves signs may not be evident for some days after the illness commences [15]. Clinical diagnosis is difficult, especially in areas where rabies is uncommon and in the early stage, rabies can easily be confused with other disease or with normal aggressive tendencies [46].

The accuracy of laboratory diagnosis becomes inconsistent when based solely on the presence of Negri bodies, because Negri bodies are found only in 40-80% of rabies cases. Along with such variable and inconsistent Negri body formation, some hematoxylin and eosin stained inclusions in the cytoplasm of neurons resemble Negri bodies but might not be rabies specific. Such pseudo Negri bodies are protein related inclusions and can lead to an initial false positive diagnosis of rabies. These cytoplasmic inclusion bodies have been described in the neurons of non-rabid cats, cattle, mongoose, woodchucks and skunks [47]. The brain of the cats, particularly, offers difficulty because of the pink staining granular material in the cells and also because the negri bodies in the pyramidal and purkinje cells of this animal are often very small [48].

The diagnosis of rabies is challenging because of the long incubation period (20–60 days on average, with rare reports of 5–6 days and up to 7 years) and the lack of specificity of early prodromal symptoms and neurologic symptoms, including paresthesias, pruritis and pain at the site of viral entry [49]. In humans, rabies often develops with a wide variety of nonspecific clinical symptoms and symptoms believed to be typical of rabies (e.g., foaming at the mouth, hydrophobia and extreme aggressiveness) are frequently not observed. Approximately 30% of human rabies cases develop in the paralytic or dumb form [50] and the overlap of symptoms with those of other infections often leads to misdiagnosis [51].

Vaccine Challenges: Vaccines are expensive and consequently, out of the reach for many people in developing countries. Nerve tissue vaccines are regrettably still used most frequently in many developing counties and they are associated with serious neurologic complications due to autoimmune disease [1]. The other challenge is that rabies related viruses have been isolated from domestic animals vaccinated against rabies.

There was also possibility of the patient developing a neuropathy (paralytic neuritis) following vaccination [52]. Post exposure vaccination is unlikely to be of value in animals, as the death usually occurs before appreciable immunity has had time to develop [15].

Problems remained with Pasteur vaccine, however, because improperly inactivated virus cause rabies and animal brain tissue induced allergic reactions leading to neuro-paralytic accidents. Moreover, perhaps most importantly, the vaccine was not very effective in cases of severe bites, such as those inflicted on the face and neck by rabid wolves and dogs [53]. The challenges and concerns associated with inactivated vaccines is their disadvantage. It is not possible to produce inactivated vaccines for all viruses, as denaturation of virus proteins may lead to loss of antigenicity [54].

Vaccinosis: Vaccinosis is the reaction from common inoculations (vaccines) against the body's immune system and general wellbeing. These reactions might take months or years to show up and will cause undue harm to future generations. Vaccinosis, which is used to describe the chronic illness that results from vaccination, should be understood as the disturbance of the vital force by vaccination that results in mental, emotional and physical changes that can, in some cases be a permanent condition [55, 56].

Chronic Symptoms after Vaccination: Chronic symptoms look very much like the acute illnesses but they are often not life-threatening unless allowed to continue for years and years. According to O'Driscoll [57], McRearden [55] and Blanco [56], symptoms after vaccination include: restless nature (suspicion of others, aggression to animals and people); changes in behavior (aloofness, unaffectionate, desire to roam, or clingy, separation anxiety, 'velcro dog', voice changes e.g., hoarseness and excessive barking, chronic poor appetite, very finicky, eating wood, stones, earth and stool); paralysis of throat or tongue, sloppy eaters and drooling; dry eye (loss of sight and cataract); destructive behavior (shredding bedding, seizures, epilepsy, twitching, increased sexual desire, sexual aggression, irregular pulse, heart failure and reverse sneezing) and restraining can lead to violent behavior and self-injury self-mutilation (tail chewing).

Anaphylactic Shock: Anaphylactic shock is the most well-known consequence, but other consequences are possible, namely types I, II, III and IV hypersensitivity reactions, which include tissue injury, arthritis, lupus and kidney and liver damage. Vaccines sensitize genetically susceptible organisms. Animals from families that are known to suffer allergic/inflammatory conditions are at most risk from live vaccines [55].

Generically Stimulations of the Body: As it has been demonstrated that a wide range of human vaccines can stimulate arthritis, it makes sense to consider, also, that animal vaccines might also stimulate this condition [57]. Glickman and Gogenesch [58] showed that vaccinated group developed significant levels of auto antibodies against fibronectin, laminin, DNA, albumin, Cytochrome C, transferring, cardiolipin and collagen in a study on the effects of routinely used vaccination protocol of commercial multivalent vaccine and rabies vaccine on the immune and endocrine system of Beagles.

According to O'Driscoll [57], this is the fundamental problem with vaccines: they are generically stimulating to the body, usually creating illness where there once was none. Some researchers have suggested that something in the vaccine could be one of the etiologies (in the genetically susceptible dog) of such diseases as cardiomyopathy, lupus, erythematosus, glomerulonephritis, etc. However, other factors other than generic reaction are also responsible for adverse reaction after vaccination.

Economic Challenges: The economic costs of rabies in a country are associated with pet animal vaccinations, animal bite investigations, conferment and quarantine of domestic animals which bite humans or which are suspected of exposure to rabid animals, salaries of animal control officers, laboratory diagnosis and treatment and consultation, public education, staff training and clerical costs [15].

The cost of the point infection control programs as a response to a raccoon rabies introduction in Ontario in 1999 was \$ 500/km^2. The costs was justified as by containing the spread of the raccoon rabies annual savings to Ontario before raccoon rabies occurred were estimated at about \$ 6 million annually, excluding pet vaccination costs [15].

Despite evidence that control of dog rabies through programs of animal vaccination and elimination of stray dogs can reduce the incidence of human rabies, The cost of these programs prohibits their full implementation in much of the developing world and in even the most prosperous countries the cost of an effective dog rabies control program is a drain on public health resources. The estimated annual expenditure for rabies prevention in the United States is over US\$300 million, most of which is spent on dog vaccinations [17].

The world production of human rabies immune globulin and equine rabies immunoglobulin is currently limited and economic factors significantly restrict the use of these products [8]. Wide spread pre- exposure rabies immunization of children in the developing countries where canine rabies is endemic and rabies immune globulin is expensive or unavailable is an ambitious and expensive prospect [1]. For comprehensive rabies control programs to run sustainably, considerable resources and practical commitment are required on an annual basis. The availability of effective vaccines for dogs is a crucial issue in many countries, most of which have to rely on importing vaccines to maintain the desired quantity. This is extremely costly. Strengthening vaccine production, at least at the regional level, or finding a way to deliver quality vaccines at subsidized prices is an important priority in developing countries [7].

Many countries lack the technical expertise to carry out mass dog vaccination programs, especially in terms of human resources. In most situations, the humane handling of community dogs for vaccination requires specialized skills. Implementing country-wide vaccination programs requires the mobilization of considerable staffing resources to cover large geographical areas. There is also a need to identify and address a generally poor understanding of the disease and of the specific control measures [7].

Each year, the disease kills about 55,000 people, almost all of them in the poorest parts of Africa and Asia and more than 7 million people receive post-exposure treatment after being bitten by a rabid animal. Treatment is just expensive and time-consuming: a full course of vaccination requires five visits to a hospital or health clinic during one month. If you live in rural Africa, can mean many hours of travel and time not working [59].

One of the critical impediments to sustaining vaccination programs is their affordability in developing countries. Implementation of bi-annual, as opposed to annual, rabies vaccination campaigns is likely to be significantly more costly and therefore less affordable. As annual vaccination campaigns repeatedly achieve coverage of around 70%, leading to a significant decline in rabies [7], annual campaigns could be sufficient in rural Africa, but further research is needed to corroborate this premise. Observations at a Central Point (CP) vaccination post indicated that more than 80% of people who brought dogs for vaccination were children aged less than 14 years and they are generally considered to be economically inactive [60].

Indeed, the global economic cost of rabies is estimated to be more than $583 million and that doesn't count the trauma that deaths from rabies inflict on families and communities [59].

CONCLUSION AND RECOMMENDETIONS

Rabies is a viral infection of all animals. Its distribution is worldwide. Rabies is important in its public health significance and also as it affects all warm-blooded animals its importance goes to those wild animals which are in great danger of extinction in the world as it causes high mortality. At the down of new millennium, rabies continues an important challenge as it was in antiquity. The vaccine that under use is nervous tissue origin in most parts of the word so as to induce a great adverse effect. Logistic problems and cultural barriers for effective dog control in many countries and the high cost of human post exposure treatment, account for much of the remaining worldwide human toll. Most deaths from the rabies occur in countries with inadequate public health resources and awareness, limited access to control, vaccine, few diagnostic facilities and almost no rabies surveillance. This condition is also seen in our county.

Based on the above facts the following recommendations are forwarded:

- ✓ The diagnostic techniques and the available vaccines must be improved.
- ✓ Cooperation and adequate support of both the human health and veterinary sector.
- ✓ Appropriate education of a population and health care professionals should be undertaken.
- ✓ All possible efforts have to be made by the government and other bodies to increase and improve public health resources and to create awareness about the disease.

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